Tutor

Dr. Jorge Echeverría López
Departament de Química Inorgànica i Orgànica

Grau de Química

Treball Final de Grau

Theoretical study of π-hole bonding
Estudi teòric d'enllaços π-hole

Oliver Loveday Rosquelles

January 2021

Universitat de Barcelona

B:KC Barcelona Knowledge Campus
Campus d'Excel·lència Internacional

Esto es seguramente cierto, es absolutamente paradójico y no sabemos qué significa, pero lo hemos probado y por tanto tiene que ser verdadero.

Benjamin Pierce

Primer de tot, agrair al Dr. Jorge Echeverría per ensenyar-me una branca de la química de gran interès i per guiar-me i ajudar-me durant tot el projecte. També agrair a la Dra. Sílvia Gómez i al conjunt del grup d'Estructura Electrònica que anàlogament m'han ajudat durant la meva estància al departament. Per acabar, agrair tota la motivació i el suport rebut per part de la família, amics i amigues, i companyes i companys de la facultat.

REPORT

CONTENTS

1. SUMMARY 5
2. RESUM 7
3. INTRODUCTION 9
3.1. π-hole interactions. 9
3.1.1. π-hole interactions. Carbonyl-carbonyl contacts. 9
3.2. Lactams. 10
4. OBJECTIVES 11
5. COMPUTATIONAL METHODS 12
5.1. Cambridge Structural Database (CSD). 12
5.2. Density Functional Theory (DFT). 13
5.3. Molecular Electrostatic Potential (MEP) analysis. 15
5.4. Natural Bond Orbital (NBO) analysis. 16
5.5. Atoms In Molecules (AIM) analysis.
Quantum Theory of Atoms in Molecules (QTAIM). 17
6. RESULTS AND DISCUSSION 18
6.1. Structural analysis of experimental lactam dimers. 18
6.1.1. Structural analysis. Hits. 18
6.1.2. Structural analysis. Distance – Angle α correlation analysis. 18
6.1.3. Structural analysis. Distance – Angle β correlation analysis. 21
6.2. Interaction Energies analysis. 22
6.2.1. Interaction Energies. Experimental cases. 22
6.2.2. Interaction Energies. Model-based cases. 23
6.2.2.1. Interaction Energies. Model-based cases. Attack angle (α) scan. 27
6.2.2.2. Interaction Energies. Model-based cases. Angle β scan. 28
6.3. Molecular Electrostatic Potential (MEP) analysis. 30
6.4. Natural Bond Orbital (NBO) analysis 32

6.5. Atoms In Molecules (AIM) analysis 33
7. CONCLUSIONS 39
8. REFERENCES AND NOTES 41
9. ACRONYMS 43
APPENDICES 45
Appendix 1: Interaction Energy-Angle β correlation analysis 47
Appendix 2: Second-order perturbation energy analysis for carbonyl-carbonyl interactions 49

1. SUMMARY

Non-covalent π-hole interactions have been of great scientific interest in recent years given their contribution to the formation of crystalline structures. Several studies have recently been conducted in order to comprehend and characterize such interactions. This work aims to understand the nature of π-hole contacts in lactam crystalline structures, since they are molecules known for their key role in the field of medicine and antibiotics.

This project has carried out both a structural and a theoretical analysis of such interactions for various lactam systems, both experimental and computational model based. A first search in the Cambridge Structural Database (CSD) has given us a first notion of the interaction nature and possible contributions involved in it, such as the orbital contribution. Analyses using Density Theory Functional (DFT) and Natural Bond Orbital (NBO) calculations have allowed us to see the orbital contribution implicated in the π-hole contact and studies using Molecular Electrostatic Potential (MEP) and Atoms In Molecules (AIM) calculations have shown us the electrostatic contribution present in such interaction.

From the data recollected it has been possible to see how these interactions present bond values that are not negligible in terms of the formation of crystalline structures. It has also been observed that their nature is not merely electrostatic because, despite being small, the orbital contribution governs some interaction parameters such as the attack angle between the donor atom and the acceptor atom.

Keywords: Non-covalent interaction, π-hole, orbital, electrostatic forces, crystalline structure, lactam, CSD, DFT, NBO, MEP, AIM, QTAIM.

2. RESUM

Les interaccions no covalents π-hole han presentat en els darrers anys un gran interès científic donada la seva contribució en la conformació d'estructures cristal·lines. Recentment s'han dut a terme diversos estudis per tal d'entendre i caracteritzar tals interaccions. Aquest treball té com a finalitat entendre la naturalesa dels contactes π-hole en estructures cristal·lines lactàmiques, donat que són molècules conegudes pel seu paper clau en aplicacions en el camp de la medicina i dels antibiòtics.

En aquest projecte s'ha dut a terme anàlogament una anàlisi estructural i teórica de dites interaccions per a diversos sistemes lactàmics tant experimentals com modelats computacionalment. Una primera cerca en la Cambridge Structural Database (CSD) ens ha donat una primera noció sobre la naturalesa de la interacció i sobre possibles contribucions involucrades en aquesta, com ara la orbitàlica. Les anàlisis mitjançant càlculs de Density Functional Theory (DFT) i Natural Bond Orbital (NBO) ens han permès veure aquesta contribució orbitàlica involucrada en la interacció, i els estudis mitjançant Molecular Electrostatic Potential (MEP) i Atoms In Molecules (AIM) ens han mostrat la contribució electrostàtica present en aquest tipus de contacte no covalent.

A partir de les dades obtingudes s'ha pogut veure com aquestes interaccions presenten uns valors d'enllaç que no són menyspreables i tenen un paper clau pel que fa a la conformació d'estructures cristal·lines. S'ha pogut observar també que la seva naturalesa no és merament electrostática (tal i com s'havia pensat fins ara) ja que, tot i ser petita, la contribució orbitàlica regeix alguns paràmetres de la interacció com ara l'angle d'atac entre l'àtom donador i l'àtom acceptor.

Paraules clau: Interacció no covalent, π-hole, orbital, forces electrostàtiques, estructura cristal·lina, lactama, CSD, DFT, NBO, MEP, AIM, QTAIM.

3. INTRODUCTION

Non-covalent interactions have been recently in the spotlight of research due to their abundance and role in many chemical and biological processes. It has also been seen that these contacts have relevant importance in crystal engineering since the play a key role in the formation of crystalline structures.

Many of these so-called weak interactions have already been studied and characterized, such as the hydrogen or the halogen bonding.

Nonetheless, some of these non-covalent interactions are not yet fully understood in terms of their nature and the factors involved in their contact strength. One of these interactions still under study is the so-called π-hole interaction, which will be the main focus of this work.

3.1. Π-HOLE INTERACTIONS

In order to comprehend this interaction, it is important first to introduce the reader to some important concepts, such as the definition of π-holes.

π-holes are molecular local regions of electron density depletion and therefore, have positive molecular electrostatic potential in the perpendicular molecular plane.

These areas are prone to exhibit interactions with electron-rich regions, forming what is known as π-hole interactions.

These interactions were thought to be solely electrostatic but recent studies have shed light on their nature and it has been observed that other contributions, such as charge transfer, have an important role in this.

This latter contribution has been observed to take place between a lone-pair and an empty π* antibonding orbital and therefore is referred as n→π*.

3.1.1. π-hole interactions. Carbonyl-Carbonyl contacts

Carbonyl groups are one of the most important groups in chemistry and biology due to their versatile behavior, where a wide range of chemical transformations and processes can be carried out, but also due to their role in intra and intermolecular interactions, such has hydrogen bonds and dipole-dipole interactions.

It is known that carbonyl groups present an electron density depletion region located on the carbon atom due to the presence of empty π orbitals. This characteristic has been recently studied

and it has been seen that this molecular region can act as a π-hole, establishing a non-covalent interaction with electron rich groups.

On the other hand, carbonyl groups can act as electron rich donor groups due to the lone pairs located in the oxygen atom. In addition, the double bond site present in the group is also rich in electron density and could probably also act as such.

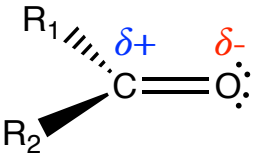


Figure 1. Scheme of the electron density regions of the carbonyl group

Therefore, this double behavior present in the nature of carbonyl groups along with its prominent role previously described, makes the carbonyl-carbonyl interaction an interesting case to study. The core of this work will be the study of carbonyl-carbonyl π-hole intermolecular interactions in lactam structures.

3.2. LACTAMS

Lactams are cyclic amides known for being biologically active therefore having an important role in the medicinal chemistry area of research, specifically in the ambit of drugs and antibiotics,[1,2] thus making them an interesting case to research in order to understand the role of the π-hole intermolecular interactions and their importance in driving the formation of crystal structures.

Better understanding of the carbonyl-carbonyl interaction present in lactam structures can lead to an improvement in drug and antibiotic manufacturing due to improving and studying better packing systems and active site enhancements.

Lactams' nomenclature is expressed as "Lactam" proceeded by a Greek-lettered prefix alphabetically ordered which indicates the ring size. Five structures are known: α-Lactam, β-Lactam, γ-Lactam, δ-Lactam and ε-Lactam (see Figure 2), where this work will be focusing on the last four cases.

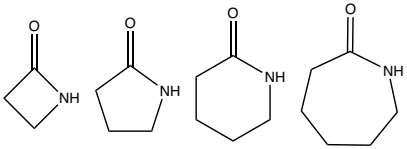


Figure 2. From left to right: β, γ, δ and ε lactam structures

4. OBJECTIVES

The main objective of this project is to study, understand and characterize the intermolecular π-hole interaction between carbonyl groups that are present in the crystal structures of lactams. Such analysis has been carried out through an exhaustive structural and computational study on different experimental and computed lactam systems. Therefore, in order to fulfill this goal, the following objectives have been set:

- The structural study of different experimental lactam systems which present carbonyl-carbonyl π-hole interactions.
- The study of the attractive/repulsive nature of the intermolecular carbonyl-carbonyl π-hole interaction.
- To carry out an electronic structure study on the π-hole interaction strength and its dependency on different structural parameters.
- To carry out a Molecular Electrostatic Potential (MEP) analysis in order to analyze the electrostatic contribution in π-hole interactions.
- To perform a Natural Bond Orbital (NBO) analysis in order to comprehend the importance of orbital charge transfer of π-hole interactions.
- To perform an Atoms in Molecules (AIM) analysis of the topology of the electron density in different calculated and experimental systems in order to understand the nature of π-hole interactions.

5. COMPUTATIONAL METHODS

Several structural and computational quantum chemistry methods and tools have been utilized in order to reach the objectives established for this project, focusing on the Cambridge Structural Database[3] (CSD) and DFT, NBO and QTAIM methods for the electronic structure calculations.

5.1. Cambridge Structural Database (CSD)

The structural study has been carried out through the Cambridge Structural Database (CSD) version 5.41, November 2019. In order to obtain the desired structures, searches have been performed with the following filters: only 3D coordinates determined crystallographic structures, not polymeric, with a R factor smaller or equal to 0.05, non-disordered systems and with no errors.

This analysis has consisted in a search for short intermolecular contacts between carbonyl groups in lactams of different n atom-ring size (from n = 4 to n = 7) with lone-pair containing donor atoms (X). The study has been performed with a top-down approach. First, all atoms from groups 15, 16 and 17 have been allowed as donor atoms, and three geometrical parameters have been determined: the contact distance between the $C_{carbonyl}$ and the donor atom (X), the angle defined by $O_{carbonyl}$ — $C_{carbonyil}$ — Donor atom (angle α) and the angle defined by $C_{carbonyl}$ — Donor atom — R (angle β) (see Figure 3).

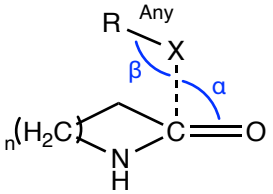


Figure 3. Parameters involved in the π-hole interaction.

Contact distances have been parametrized to be shorter than the sum of the van der Waals radii of the atoms involved plus 0.3 Å, and have been normalized using the van der Waals radii proposed by Alvarez[4].

Once all data has been collected, a case-by-case study has been done with emphasis on the R—O systems as donor groups, distinguishing between monocoordinated and dicoordinated oxygen molecules. This work has focused on the first case since carbonyl-carbonyl interactions are the corner stone of this study.

All structural searches have been done underestimating hydrogen bonds between the carbonyl group and alcohol and amino groups, in order to obtain results as accurate as possible, since these electrostatic interactions are highly frequent in these kinds of systems and can distort the analysis results.

Experimental cases studied in this work have been obtained through CSD and are given throughout the text as six-letter refcodes (e.g., UVWXYZ).

5.2. Density Functional Theory (DFT)

In order to study the electronic structure of the systems in this work, quantum chemistry calculations have been done at the DFT level.

DFT is an *ab initio* modelling method based on computational quantum mechanics which allows us to predict properties, mainly ground state energies, from simple molecular structures to many-body systems, and to study the nature of chemical bonding.

The theoretical fundament of these type of methods was grounded in the Hohenberg-Kohn theorems, the first of which proves that in a many-electron system, the ground-state properties are uniquely determined by the electron density, dependent on only three spatial coordinates (three variables), and the second theorem defines that for each system there is associated an energy functional which is minimized at the ground-state electron density.

These theorems where later improved by the introduction of the Kohn-Sham equations and Koopmans' theorem. Nevertheless, these theorems don't come up with the form of the energy functional. Therefore, there have been set a range of approximate functionals which are known to give accurate results in a wide case of chemical computational studies.

As mentioned above, the variable dependency (only three coordinates) of the DFT energy functional makes the costs for computational calculations relatively low when compared to other *ab initio* methods, such as the widely used Hartree-Fock (HF) and post-Hartree-Fock methods based on the total wave function. In comparison, the functional for a N electron system in HF methods presents 3N variables in order to calculate the total energy.

When calculating the ground state energy, DFT methods allow us to refine the calculations by introducing other types of functionals such as the exchange-correlation energy functional (xc), which has in consideration the electronic correlation of the many-electron system. The most widely xc functionals used are the LDA, the GGA (and its hybrid analog) and the B3LYP.

For further knowledge about DFT, literature *Density Functional Methods in Chemistry* by Jan K. Labanowski and Jan W. Andzelm is highly recommended.

In our study, structural optimization and electronic structure calculations have been performed using Gaussian09,[5] with the M06-2X functional and def2-TZVP basis set. The combination of the functional and the basis set used in this work have shown to perfectly fit when it comes to the computational study of non-covalent interactions. Despite not having empirical correction for dispersion, it has been highly parametrized with non-covalent systems.[6]

Structural optimization of modelled systems has been carried out through an initial proposed geometry as shown in the figure below (see Figure 4) and have not been confirmed to be true minima by frequency calculations due to the time limitations of this work.

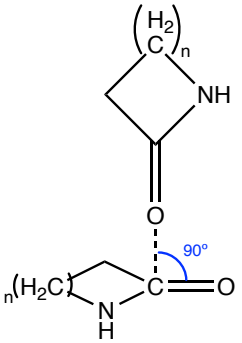


Figure 4. Initial geometry used in the structural optimizations.

Interaction energies have been calculated by the supermolecular approach as $\Delta E(AB) = E_{AB} - (E_B + E_A)$ and the basis set superposition error (BSSE) has been corrected via the counterpoise method (CP).[7]

5.3. Molecular Electrostatic Potential (MEP) analysis

Molecular Electrostatic Potential (MEP) analysis has been taken in consideration for this project since such analysis expressed on the van der Waals isosurface has been proven to be a very useful approach when it comes to the prediction of molecular reactivity when nucleophilic and electrophilic species are involved.[8,9]

Nevertheless, such analysis brings down the nature of the interaction to only electrostatic forces, but it has been proven to be useful when it comes to the reactivity study of molecular π-hole and other non-covalent interactions.[10]

The main objective of this section of study is to analyze the electrostatic contribution involved in the π-hole interaction. Therefore, the simplification explained above is valid since other possible contributions will be studied via other tools.

The molecular electrostatic potential is represented in the form of an isosurface, in our case the correspondent to the van der Waals radii of the atoms of the molecular structure, and regions are represented in different colors. Regions with high electron density, which tend to be electron-rich species, are represented in red and present negative MEP values. Regions with depletion of the electron density, associated with electron-deficient species, are represented in blue and present positive MEP values.

MEP surfaces have been built and represented on the 0.001 Å isosurface with Gaussian/GaussView.[5]

5.4. Natural Bond Orbital (NBO) analysis

A comprehensive NBO analysis has been carried out to characterize orbital-orbital interactions in different lactam dimers. This method is frequently used in order to characterize charge transfer interactions of different kinds of systems and provides much insight into π-hole interactions.[11,12]

This computational method protocols partition electron density from diffuse molecular orbitals into localized Lewis-type orbitals, whence the stabilization energy between donor-acceptor group can be calculated.

$$AO \longleftrightarrow NBO \longleftrightarrow MO$$

The stabilization energy, also named NBO energy, provides us with information about the favorability of the interaction. Therefore, values > 0 mean a favorable stabilization interaction between the two groups and, subsequently, a contribution to the overall stability of the system.

These energies are calculated by means of second-order perturbation theory analysis of Fock matrix in NBO basis.

For further depth on the subject, the literature *Discovering Chemistry with Natural Bond Orbitals* by Frank Weinhold and Clark R. Landis is recommended, since this has been, mostly, the main source of information used in this work when it comes to comprehend the theoretical background of NBO and its analysis.

In this project NBO analysis has been performed with the NBO 3.1 program which is included in Gaussian09, with the M06-2X functional and def2-TZVP as basis set.

5.5. Atoms In Molecules (AIM) analysis. Quantum Theory of Atoms in Molecules (QTAIM)

The topology of the electron density of experimental and computed systems has been explored by means of Bader's Quantum Theory of Atoms in Molecules.[13]

QTAIM is a quantum chemistry model which approaches atoms in molecules as of open systems (where charge and momentum with neighbor atoms are free to exchange) that constitute the total system (molecule). Also, the definition of the bonds, that link the atoms in order to form the structure, has to be made. This theory recovers the molecular structure hypothesis, which states that a molecule is a collection of atoms, each with a characteristic set of properties, that are linked by a network of bonds.

However, this generalization can only be accomplished if a certain boundary condition is satisfied, which demands that in the gradient vector field of the charge density, its flux has to vanish at every point of the surface that bounds an open system. This condition leads to the partitioning of a molecular system into a set of separated spatial regions (chemical atoms).

Therefore, this theory defines the structure of a molecular system and its chemical bonding based on the topology of the electron density.

If further study about this topic is desired, the literature *Atoms in Molecules: A Quantum Theory* by Richard F. W. Bader is recommended.

The charge density topology allows us to study all sorts of different chemical systems and its bond paths, allowing us to study weak intermolecular interactions in organic crystal systems such as π-hole interactions.

In this work, AIM analysis of the electron density topology has been carried out with the AIMAll program[14] at the same level of theory as DFT and NBO calculations (M06-2X/def2-TZVP).

In this study, Bond Critical Points (BCPs) have been the matter of study and associated parameters such as electron density (ρ), Laplacian of the electron density ($\nabla^2\rho$), the total energy density (H) and the delocalization index (DI(A,B)). Relevance of each parameter is described in Section 6.5 AIM analysis.

6. RESULTS AND DISCUSSION

6.1. Structural analysis of experimental lactam dimers

Following the procedure presented in section 5.1, here there will be shown the results obtained from the crystal structures analysis. This discussion has been divided into three subsections corresponding to the hits obtained, distance-angle α correlation analysis and distance-angle β correlation analysis.

6.1.1. Structural analysis. Hits.

Searches corresponding to crystal structures for lactam molecules have given the following results presented in the form of a table (see Table 1). This includes the total number of crystal structures obtained and the number of hits obtained corresponding to short X···$C_{carbonyl}$ contacts for each lone-pair-containing donor atom:

Lactam	Total structures	Hits N	Hits P	Hits O MC	Hits O DC	Hits S	Hits F	Hits Cl	Hits Br	Hits I
β-Lactam	113	7	0	66	23	9	3	7	4	0
γ-Lactam	876	105	1	677	109	19	23	37	24	3
δ-Lactam	148	23	0	88	21	6	2	5	8	5
ε-Lactam	53	9	0	34	7	5	2	3	2	1

Table 1. Total structures obtained from the CSD with its correspondent X···C contact hits.

MC = Monocoordinated
DC = Dicoordinated

As it can be observed, contacts involving nitrogen and oxygen (mostly monocoordinated) are predominant in these kinds of structures, which is expected due to their importance in chemical and biological processes.

6.1.2. Structural analysis. Distance - Angle α correlation analysis.

Correlation between distance and the attack angle (α) of the interaction between lone-pair-containing group and the carbonyl carbon of lactams (X···C=O) has been analyzed. In general, a tendency can be seen where angle α gets close to 100º as the interaction distance decreases (see Figure 5, normalized distance populations are included).

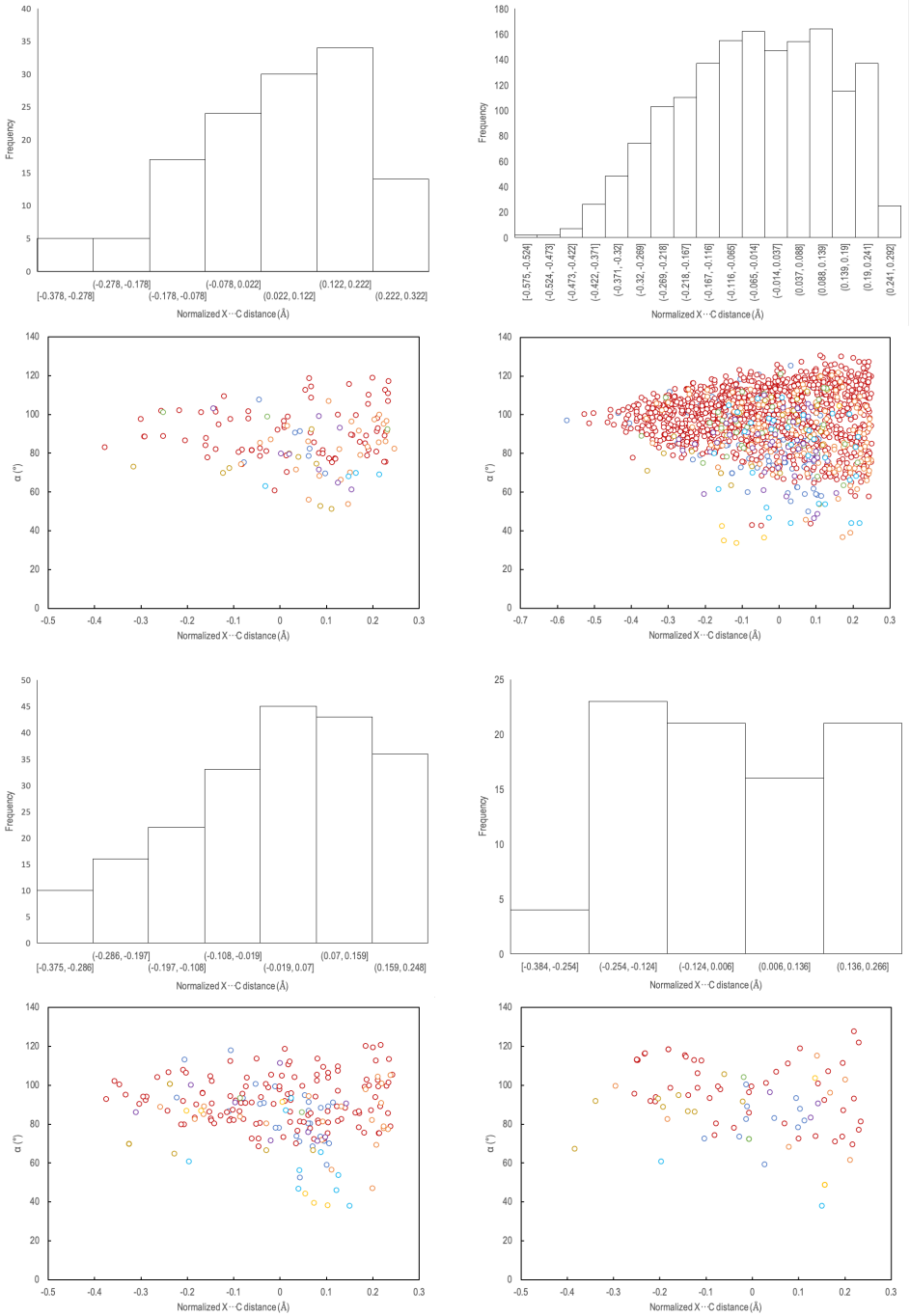


Figure 5. Distance population histogram and X···C distance - α correlation. Top: β-lactam and γ-lactam. Bottom: δ-lactam and ε-lactam. Donor atoms have been represented with different colors: N (dark blue), P (black), O MC (garnet), O DC (salmon), S (brown), F (green), Cl (purple), Br (light blue), I (yellow).

This behavior has been seen before in lone-pair - carbonyl interactions of this kind[15,16] and is related to the Burgi-Dunitz trajectory for a nucleophilic attack.[17,18] The fact that this trajectory is observed means that the n→π* interaction presents an orbital contribution, since the π* orbital from the $C_{carbonyl}$ is perpendicular to the double-bond from the carbonyl group and can only be filled from above, leading to a favorable angle attack of around 100º.

Since this work is mainly focused on carbonyl - carbonyl interactions these are highlighted here below (see Figure 6).

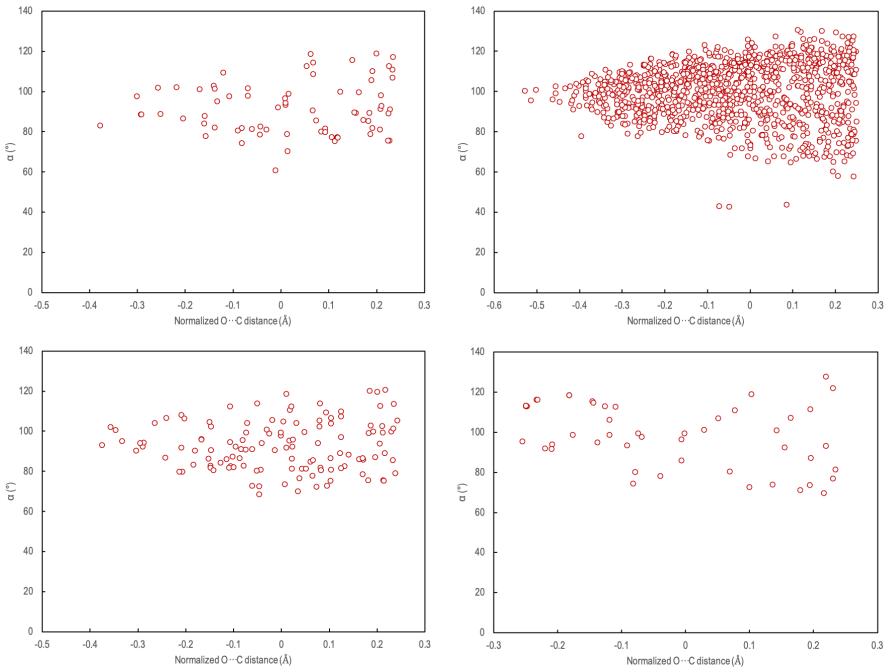


Figure 6. Distance - attack angle (α) correlation for carbonyl-carbonyl interactions. Top: β-lactam and γ-lactam. Bottom: δ-lactam and ε-lactam.

For carbonyl - carbonyl interactions it is observable that for long-distanced contact, angle range goes from 60 to 140º. But as distance is shortened, in all cases minus ε-lactam structures, it is clearly seen that the attack angle tends to 100º, such as Burgi-Dunitz predicted in their studies.

6.1.3. Structural analysis. Distance - Angle β correlation analysis.

Distance and angle β correlation is not expected to be as defined as distance — angle α correlation but secondary interactions such as N—H···O=C are expected due to proximity between groups since ring sizes are relatively small.

Results (see Figure 7) have shown that in carbonyl-carbonyl intermolecular interactions there is a general tendency where β angle is located in a range between 80 and 180º. This information will be later studied in section 6.2.2.2 where a scan angle will be performed in model-based cases in order to study the nature of such behavior.

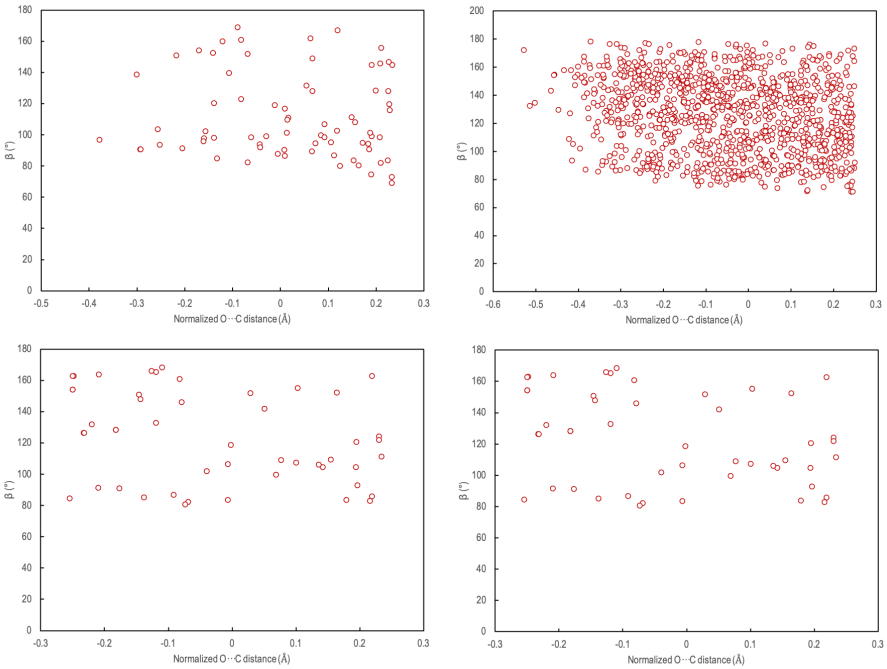


Figure 7. Distance - angle β correlation for carbonyl-carbonyl interactions. Top: β- lactam and γ-lactam. Bottom: δ-lactam and ε-lactam.

6.2. Interaction Energies analysis

As described in section 5.2, DFT calculations are a good method for describing weak interaction energies such as those involved in π-hole interactions. The objective of this section is to try to understand the nature of these and to analyze certain dependencies such as the attack angle (α) and angle β by means of DFT calculations and simple systems of model-based lactam dimers previously optimized.

6.2.1. Interaction energies. Experimental cases.

The first step in this analysis has consisted of the study in interaction energies of experimental crystal structures extracted from the Cambridge Structural Database. Five β-lactam systems have been selected (see Figure 8) and the intermolecular interaction has been calculated.

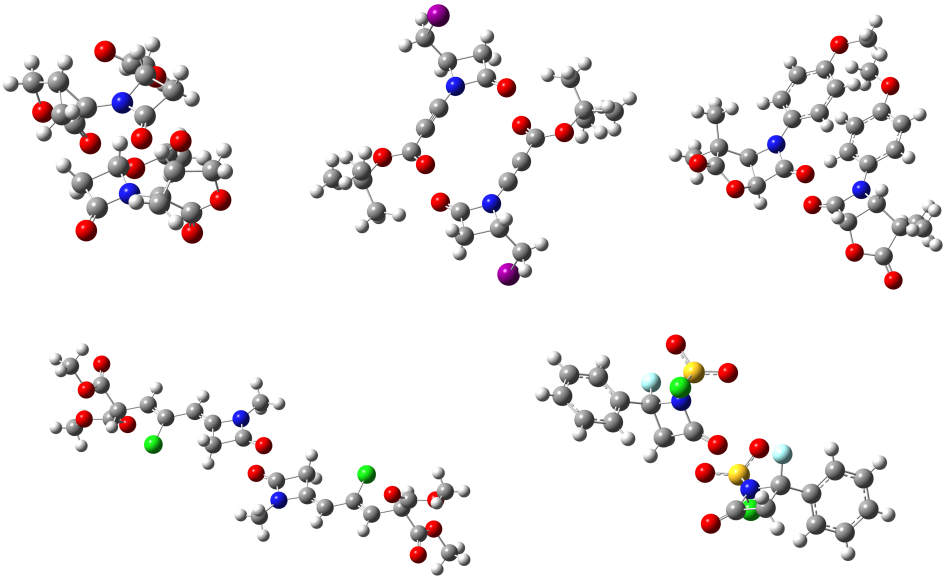


Figure 8. Experimental β-lactam structures. Top: BOVFOH, DEDSIO and FIYCOG. Bottom: KUJJOO and UMUNAS. Color code: H (white), C (gray), N (blue), I (purple), Cl (green), S (yellow), F (light blue).

Interaction energies have been summarized in the table below (see Table 2).

RefCode	$d_{O\cdots C}$ (Å)	α (º)	ΔE_{int} (kcal·mol^{-1})
BOVFOH	3.100	101.2	-9.04
DEDSIO	3.226	75.5	-9.02
FIYCOG	2.978	88.6	-14.02
KUJJOO	3.303	96.6	-4.65
UMUNAS	3.131	101.3	-5.39

Table 2. Interaction energies obtained from experimental systems and their related parameters.

This is a qualitative study since these different crystal structures present other intermolecular interactions (as can be seen in Figure 8) which have not been taken into consideration, therefore no $d_{O\cdots C}$ - α correlation can be observed.

Nevertheless, this first analysis shows that π-hole interactions have an attractive nature, as it has already been observed in similar cases[15,19,20,21,22]. This allows us to take a step further and interaction analysis has been made with computed model-based lactams in order to study more precisely π-hole interactions.

6.2.2. Interaction energies. Model-based cases.

Interaction energies of computed lactam dimers have been analyzed by means of DFT calculations in order to understand π-hole interactions in more depth.

Firstly, five different lactam systems have been created using the program Avogadro[23] with an initial carbonyl-carbonyl geometry orientation of α = 90º (see Figure 4).

Secondly, a structure optimization has been done and with the resultant dispositions (see Figure 9), interaction energy calculations have been made for each case and are summarized in Table 3.

As it has been noted in section 5.2, these optimizations have not been confirmed to be true minima by frequency analysis due to time limitations of this project. This limitation doesn't invalidate the results obtained here and further along, but for further studies it is highly recommended to carry out calculations with fully optimized structures in order achieve more accurate results.

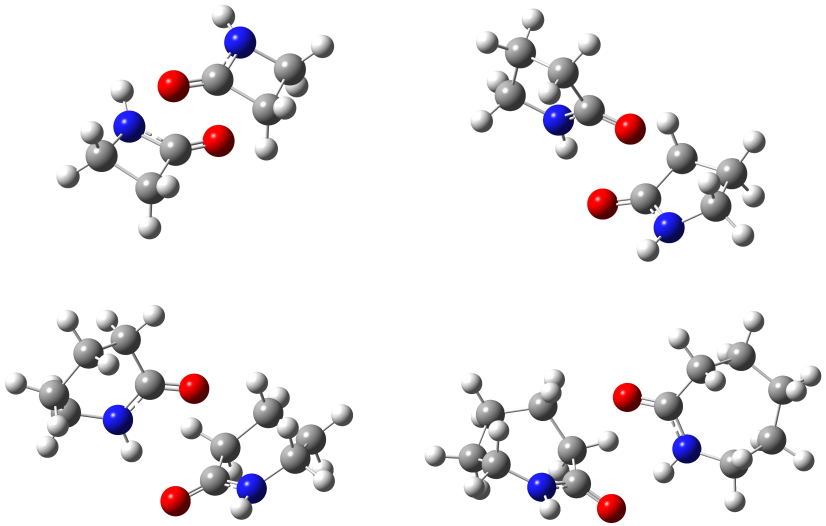


Figure 9. Resultant optimized structures of model-based lactam dimers. Top: β-lactam and γ-lactam. Bottom: δ-lactam and ε-lactam.

	$d_{O\cdots C}$ (Å)	α (º)	β (º)	ΔE_{int} (kcal·mol^{-1})
β-lactam	3.022	101.0	79.0	-9.39
γ-lactam	2.991	100.4	105.0	-11.51
δ-lactam	2.908	100.4	108.8	-11.79
ε-lactam	3.052	92.5	110.9	-10.24

Table 3. Interaction energies and parameters for the model-based optimized structures.

Optimized molecules show interesting results. A general tendency can be observed where the carbonyl group that performs the nucleophilic attack is located slightly towards the center of the ring. This is due to the presence of hydrogen atoms in the cyclic structure whose resultant interaction favors the overall interaction between the two molecules.

Another remarkable phenomenon observed is that all molecules except β-lactam dimer have shown the same carbonyl-carbonyl orientation, where the π-hole interaction is given in addition to an intermolecular hydrogen bond. The presence of an additional interaction between molecules stabilizes the overall system, therefore β-lactam dimer presents a more positive interaction energy (weaker interaction).

However, this latter case presents an interesting outlook also observed in real crystal structures such as DEDSIO, FIYCOG and KUJJOO (see Figure 8) where the π-hole interaction is an anti-parallel back bonding between both carbonyl groups, which will be further analyzed.

Focusing now on structural parameters, it can be observed that these model-based systems show angle values which perfectly fit the Burgi-Dunitz trajectory for a nucleophilic attack.[17,18]

Since β-lactam dimer shows a different behavior, correlation analysis between interaction energy and contact distance and attack angle has only been applied in the other three cases. It can be observed that there is a direct relation between the interaction energy and the contact distance.

As the distance between the atoms involved in the interaction increases, interaction energy diminishes, as can be observed, at an exponential rate (see Figure 10). Nonetheless, only three values have been carried out in this study and the exponential behavior cannot be confirmed. Further analysis should be taken into consideration in order to consolidate such affirmation.

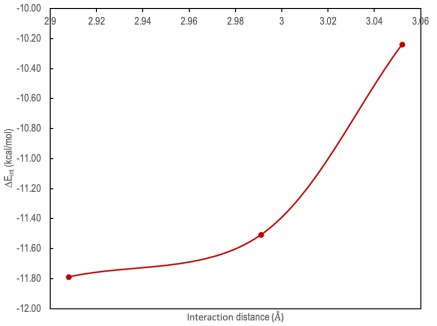


Figure 10. Distance-interaction energy correlation for model-based lactam systems.

In order to ensure in a qualitative way that optimized molecules are valid models for further analysis, forced optimizations have been carried out.

These optimizations have consisted in getting as a starting point another possible geometric orientation: in the case of the β-lactam system the starting geometry has been the one obtained form the optimization of the other three dimers, and for these dimers the starting geometry has been the anti-parallel resultant geometry from the first case.

The results obtained are summarized in Table 4 and show that for all cases, except β-lactam dimer and ε-lactam (which has not converged), the interaction energy is more positive (weaker interaction) than the non-forced optimizations.

Lactam dimer	ΔE_{int} (kcal·mol^{-1})
β-lactam	-14.45
γ-lactam	-9.77
δ-lactam	-9.95
ε-lactam	-

Table 4. Interaction energies for forced model-based systems.

β-lactam's forced optimized resultant intermolecular interaction energy seems to be more negative (more stable structure) when compared to the non-forced optimization. This is due to the resulting systems not presenting lone-pair - carbonyl interaction but intermolecular hydrogen bonds (see Figure 11).

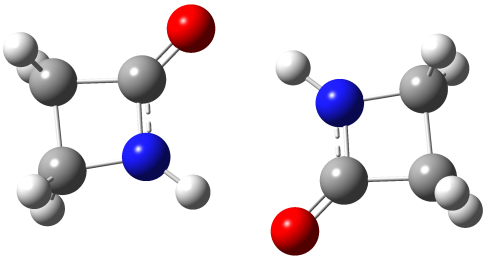


Figure 11. Forced model-based β-lactam system. No carbonyl-carbonyl interaction is observed.

Therefore, these results confirm that, even though the resultant geometries obtained from the initial optimization have not been confirmed to be true minima, these must be close to this scenario and are equally valid as references for this study.

6.2.2.1. Interaction energies. Model-based cases. Attack angle (α) scan.

A scan of the attack angle (α) has been done in the case of the β-lactam dimer in order to understand the relation between the interaction energy and the attack angle.

A starting geometry has been modeled, which has consisted in getting the anti-parallel resultant orientation obtained previously from optimization and perfectly aligning both molecules involved (fixing the interaction distance, angles α and β, which in this case are equivalent, have been set at 90º and the dihedral angle between molecules has been set to 0º, see Figure 12).

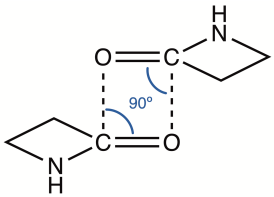


Figure 12.Starting geometry for attack angle (α) scan.

From this geometry a scan has been made modifying values of angle α from a range between 60 and 120º, in intervals between 10 and 20º. Resultant energies have been tabulated (see Table 5) and graphically represented (see Figure 13).

Angle α (º)	**ΔE_{int} (kcal·mol^{-1})**
60	0.15
80	-5.99
90	-8.12
100	-9.33
110	-5.93
120	22.89

Table 5. Resultant interaction energies from the attack angle (α) scan

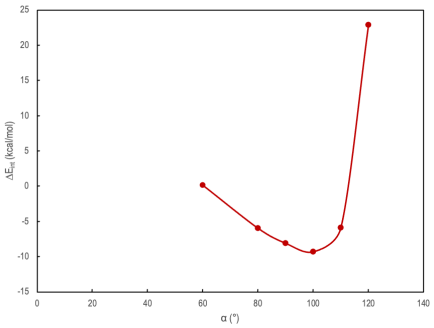


Figure 13. Attack angle (α)-distance correlation for model-based β-lactam system.

As can be observed from the results, as α value is increased, interaction energy diminishes (more stable system, stronger interaction), peaking at 100º, where the energetical value gets as negative as it can. Past this angle value, interaction energy grows exponentially which results in highly unstable systems. This is due to the close proximity between both molecules which results in a repulsive intermolecular interaction that wants to ward off one molecule from the other.

The fact that for α = 100º the interaction energy is the most favorable coincides, once again, with the Burgi-Dunitz trajectory for a nucleophilic attack.[17,18]

This analysis has only been applied for the system described above due to the molecule orientation. The other lactam dimers have not been able to be studied due to steric hindrance between the carbonyl group and the amine group involved in the intermolecular hydrogen bond (see Figure 9).

6.2.2.1. Interaction energies. Model-based cases. Angle β scan.

As it has been seen throughout this work, angle β has some interesting tendencies therefore resulting in an interesting parameter to analyze.

For model-based cases, the first hypothesis is that this angle is related to the intermolecular N—H···O=C interaction (see Figure 9) and the behavior expected is that the overall interaction energy will diminish as the angle β increases (hydrogen bond is weaken), due to a distance increase between the amine and carbonyl group.

This angle is found generally in a range between 80 and 180º, as seen in searches done in section 6.1.

The scan of the β angle has been applied to all model-based molecular structures using a similar starting geometry system methodology as for the attack angle scan, getting as reference the modified optimized systems from section 6.2.2 (interaction distance has been fixed, angle α has been set at 90º and the dihedral angle between molecules has been set to 0º. In this case, angle β has not been strictly defined to one value).

The angle analysis has been done in a range between 90 and 180º, each specific to the modelled system. The results obtained for each computed dimer have been tabulated and plotted (see Appendix 1 Table A1, Figure 14).

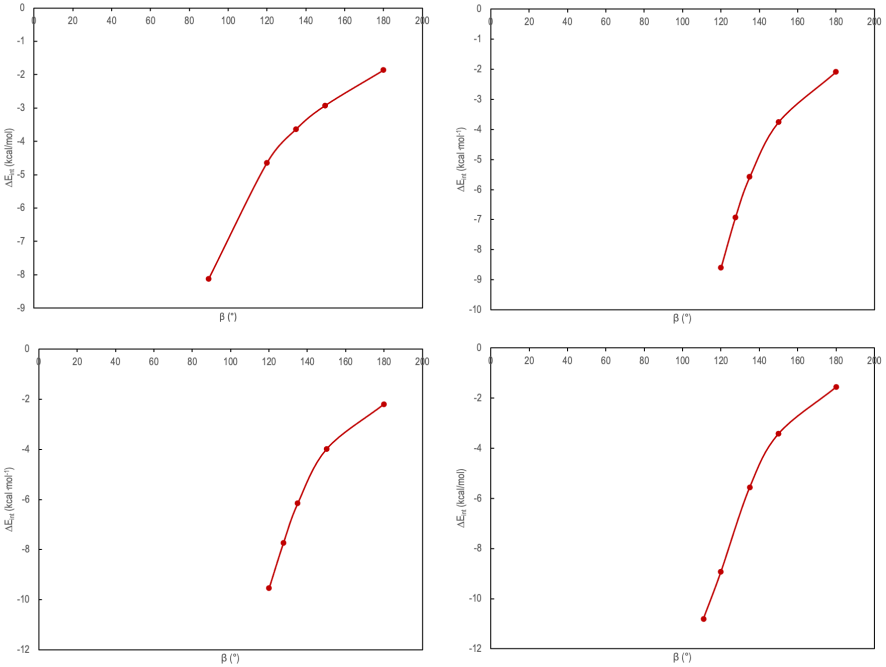


Figure 14. Angle β-interaction energy correlation for model-based lactam systems. Top: β-lactam and γ-lactam. Bottom: δ-lactam and ε-lactam.

From the results obtained we can observe how the proposed hypothesis is fulfilled. As expected, for simple systems like these, where there are no functional groups that could come into play with additional intermolecular interactions, angle β is tightly related to the hydrogen bond between molecules.

As it can be observed, initial angles in the case of β, δ and γ lactam systems do not match with the β angles obtained from the initial optimization (see Table 3).

For the first case this decision has been made in order to work with the same system when it comes to the overall angle scan sections.

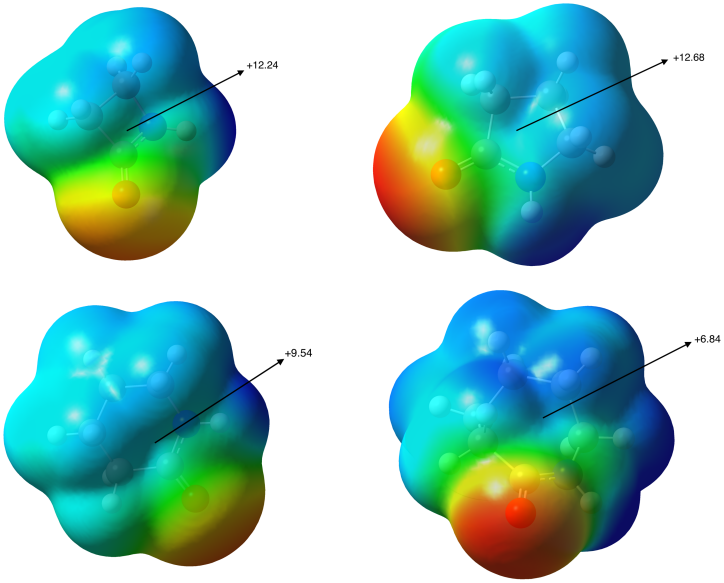
For δ and γ lactam dimers, things have gone a bit differently, since optimized molecules have been partially rearranged, some intermolecular distances such as the one related to the N—H···O=C interaction have been slightly modified. For these two cases the resultant hydrogen bond interaction distance has been so diminished that atoms where so close to each other that repulsive interaction has been observed. Therefore, these values have been considered faulty and higher value initial angles have been used.

6.3. Molecular Electrostatic Potential (MEP) analysis

As it has been described in section 5.3, MEP is a useful tool in order to study the electrostatic forces involved in π-hole interactions.

MEP isosurface has been carried out in all model-based systems and in four experimental cases have been selected in order to understand the electrostatic contribution and its role in carbonyl-carbonyl interactions.

Results represented in Figure 15 highlight the electron density depleted region corresponding to the π-hole. MEP values are expressed in kcal/mol.



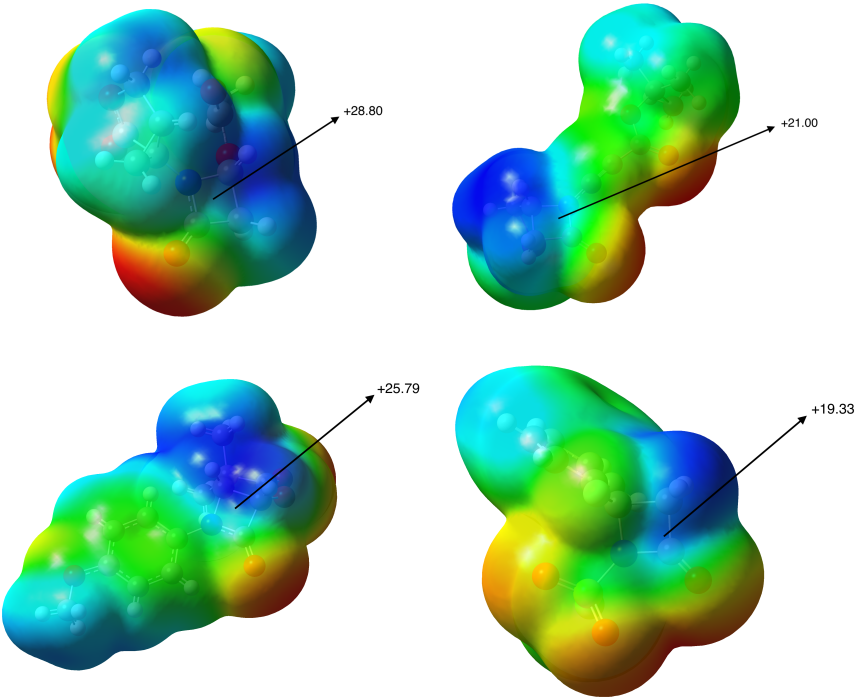


Figure 15. MEP maps for model-based and experimental dimers. Red indicates electron-rich regions and blue electron-deficient regions. Energy values are expressed in kcal/mol. From top to bottom: β-lactam and γ-lactam, δ-lactam and ε-lactam, BOVFOH and DEDSIO, FIYCOG and UMUNAS.

It can be seen that all molecules present a region of electron density depletion located in the carbon atom of the carbonyl group corresponding to the π-hole. Model-based computational systems present a relatively small surface potential value ($\bar{V}_{s,max} \sim 10.32\ kcal/mol$) and experimental dimers present an average surface potential value of $\bar{V}_{s,max} \sim 23.70\ kcal/mol$ which is consistent with results obtained from other π-hole interaction studies.

A hypothesis for the MEP value difference between model-based and experimental results can be due to the fact that the amine group for all experimental cases is totally substituted causing some sort of electron-drawing effect which favors a depletion of electron density around the carbon atom of the carbonyl group.

These regions with positive MEP values located above the carbon atom in the carbonyl group showcase the affinity of these groups to interact with electro-rich species, in our case the oxygen atom contained in another carbonyl group, in the form of an electrostatic interaction.

6.4. Natural Bond Orbital (NBO) analysis

MEP analysis has shown that there is an electrostatic contribution in π-hole interactions, but CSD and Interaction energies analyses have shown there is also an orbital contribution since geometric orientations due to the interaction follow the Burgi-Dunitz trajectory, which is associated to orbital charge-transfer. Therefore, in order to study this orbital contribution, the orbitals involved and their related charge-transfer process, NBO analysis has been seen to fit for such interaction and it has been performed both in experimental (see Table 2) and model-based cases (see Table 3).

For practically all systems, a prominent n→π* charge transfer interaction can be observed between a lone pair of the oxygen into an empty π antibonding (π*) orbital of the carbonyl.

In some systems, such as the model-based β-lactam and the experimental structure KUJJOO, which present an anti-parallel carbonyl-carbonyl interaction, it has been observed that the charge transfer interaction involved is given by π→π* orbitals from both double bonds present in the groups.

Another interesting case is the one that is present in experimental systems such as DEDSIO and FIYCOG, which also present an antiparallel carbonyl-carbonyl orientation, but they present both n→π* and π→π* charge transfer interactions.

Second-order perturbation energies for carbonyl-carbonyl interactions have been tabulated (see Appendix 2, Table A2).

Energies obtained from carbonyl-carbonyl interaction in lactam systems are on par with other similar case such as the same interaction-type given in peptide structures.[16]

Additional observation from this analysis is that systems such as model-based γ, δ and ε lactam systems with present N—H···O=C interactions where both oxygen lone-pair (n) and π orbital from the carbonyl group are involved with the antibonding orbital related to the N—H bond.

These interactions have given second-order perturbation energies from around 2.5 to approximately 4.0 kcal/mol, which are about three times higher than the values obtained with the carbonyl-carbonyl interactions.

For computed systems, this last observation together with the presence of additional π→π* orbital interactions (in the β-lactam case) can be related to the results obtained from the angle β scan: as the angle is increased, interaction energy is diminished.

6.5. Atoms in Molecules (AIM) analysis

Atoms in Molecules (AIM) analysis of both experimental (see Table 2) and model-based dimer structures (see Table 3) has been carried out.

Methodology followed in this section has consisted in the generation of wavefunction files corresponding to the molecular electronic configuration for each optimized and experimental dimer system, which allow us to study the electron density topology of the system and the interactions involved.

These output files have been run in AIMAll software[14] and from its results, Bond Paths (BPs) and Bond Critical Points (BCPs) have been taken in this study. At the BCPs, several parameters have been studied, these being the electron density (ρ), the Laplacian of the electron density ($\nabla^2\rho$), the total energy density (H) and the delocalization index between the oxygen and the carbon atom (DI(O,C)).

Electron density (ρ) at BCPs gives us information about the nature of the interaction. Positive electron density values imply electron exchange; therefore, a favorable interaction is taking place. For non-covalent interactions, slightly positive electron density values are expected due to their weak nature.

Laplacian of the electron density ($\nabla^2\rho$) at the BCPs is a measure of the curvature of the electron density at the bond critical point (BCP).

The electronic total energy density (H) can be described as

$$H = G + V$$

where G and V are, respectively, the kinetic and potential energy densities given at the BCP. Close to zero positive values indicate that it consists of a closed-shell contact, therefore will be expected in our results.

Another parameter related to the total energy density is the kinetic-potential energy ratio (|V|/G). It has been seen that this ratio is related to the interaction strength.[24] Therefore, ratio values < 1 are associated to weak interactions and values > 1 correspond to strong interactions. In our case, since we're studying a non-covalent interaction, ratio values < 1 are expected.

Delocalization index (DI(A,B)) between two atoms (A and B, in our case A = oxygen (donor atom) and B = carbon (acceptor atom)) involved in a interaction in a BCP is the measure of the number of electron pairs shared by these two atoms and it can relate to the bond strength.[25,26]

For covalent interactions DI values tend to be around 2, since 2 electrons are shared. For weak non-covalent interactions, such as our case, it is expected to get values between 0 and 1.

AIM bond-path graphs can be seen in Figure 16 and parametric results for the π-hole interactions have been tabulated (see Table 6).

Experimental dimers have not shown carbonyl-carbonyl π-hole BCPs. Therefore, for these cases results have not been conclusive and no analysis has been made.

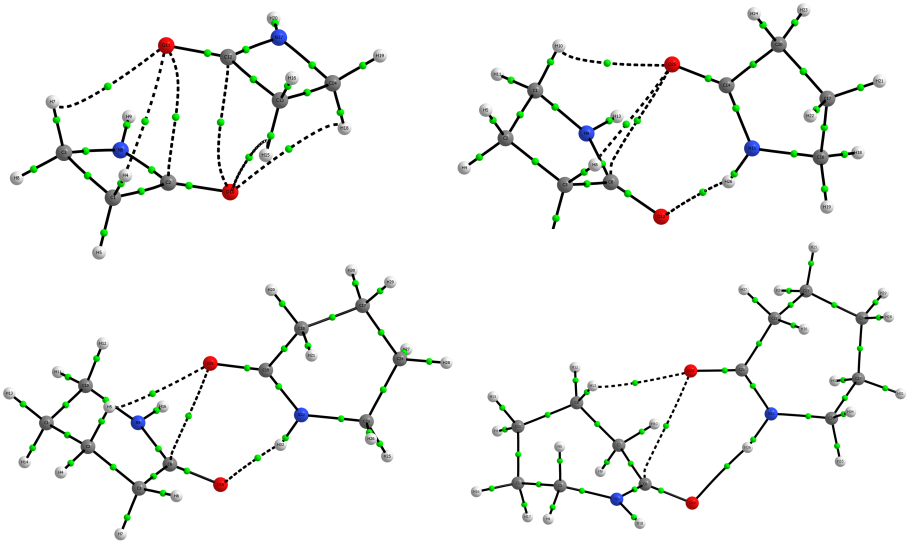


Figure 16. Bond paths and BCPs (green) for model-based systems. Bond paths associated with the intermolecular interaction are highlighted with a discontinued line. Top: β-lactam and γ-lactam. Bottom: δ-lactam and ε-lactam.

C=O···C=O interaction	ρ	$\nabla^2\rho$	G	V	H	|V|/G	DI(A,B)
β-lactam	0.0087	0.0337	0.0070	-0.0056	0.0014	0.800	0.0169
γ-lactam	0.0089	0.0347	0.0072	-0.0057	0.0015	0.792	0.0191
δ-lactam	0.0100	0.0380	0.0079	-0.0064	0.0015	0.810	0.0261
ε-lactam	0.0079	0.0297	0.0062	-0.0050	0.0012	0.806	0.0187

Table 6. BCP parameters calculated for carbonyl-carbonyl intermolecular interactions in model-based lactam structures.

For the model-based structures (Figure 16), AIM results show the π-hole interactions along with other bond paths. C—H···O=C and N—H···O=C intermolecular interactions can be observed and are expected, as seen in sections 6.2 and 6.4, which have already been described through the text as hydrogen bond interactions that contribute to the overall stabilization on the molecular system.

The results obtained from the AIM analysis (see Table 7) confirm the predictions made at the beginning of this section.

Electron density values have shown similar slightly positive values in all five dimers; therefore, we can assume that there is some sort of charge transfer contribution involved in the contact and that this consists of a weak contact.

Laplacian of the electron density ($\nabla^2\rho$) is better understood when contour representation is plotted (see Figure 17). Red contour lines represent negative regions with local charge concentration (high electron density).

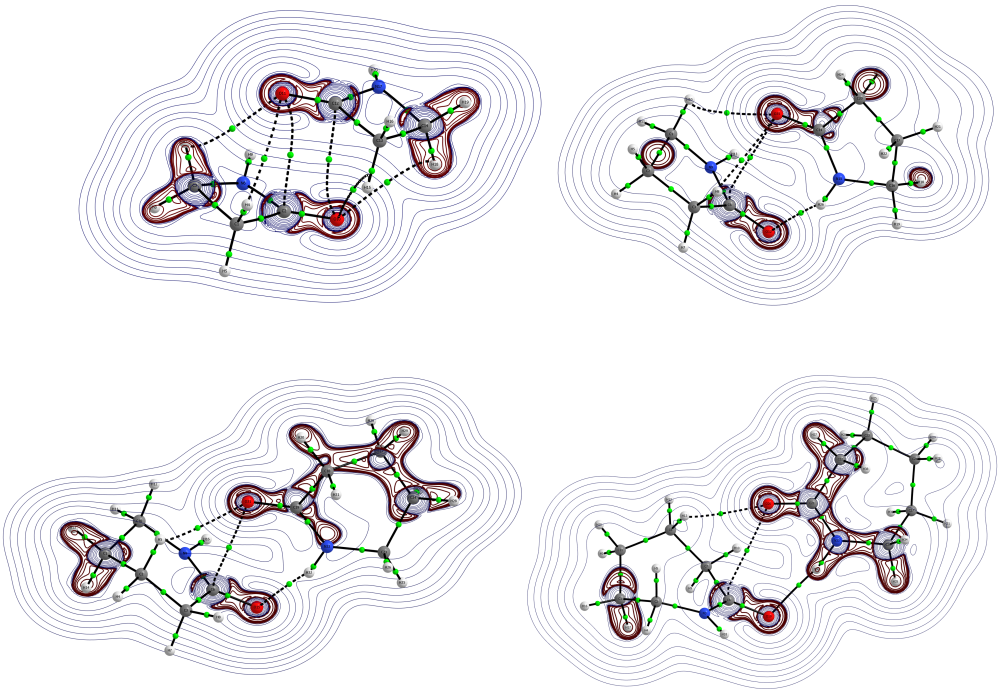


Figure 17. Laplacian of the electron density for model-based lactam systems.
Top: β-lactam and γ-lactam. Bottom: δ-lactam and ε-lactam.

The Laplacian of the electron density topology extracted from the plots suggests high concentrations of red contour lines around the oxygens contained in the carbonyl groups and the bond that configurates this group, indicating an accumulation of local charge around it. This makes sense since these oxygens contain two electron lone pairs and the carbonyl bond is a double bond, meaning that high electron density is expected around them. On the other hand, carbon in the carbonyl groups present positive holes (blue contour lines) which can relate to the resultant electron-deficient configuration when forming a carbonyl group.

Therefore, it can be assumed that negative regions such as the oxygen side of the carbonyl groups will have affinity to form some sort of an electron-exchange contact with positive regions like the carbon side of another carbonyl group.

Focusing now on the energy parameters, the electronic total energy density for the model-based systems shows positive values close to zero, meaning that all systems are closed-shell, which has been assumed since the beginning of this study.

The other energy-related parameter that provides more information on the π-hole interaction is the energy ratio (|V|/G). The resultant ratio values have an average value of ~ 0.8 and confirm that the interaction studied is a weak contact.

The last parameter to comment on is the delocalization index (DI(O,C)). Results show an average value of ~ 0.02. In simple words it could be explained as only 0.02 electron pairs are shared in these intermolecular interactions, which is consistent considering the fact that we're studying a non-covalent interaction where it has been seen throughout the whole theoretical study that this is a weak but prominent contact.

All these relatively small-valued results obtained from the AIM analysis coincide with similar studied cases[27,28] and show a solid correlation which glimpses that electron exchange contribution is relatively low and that the $n \rightarrow \pi^*$ interaction has a prominent electrostatic contribution due to the high electron density differences between the oxygen containing the lone pairs and the carbonyl electron-deficient.

7. CONCLUSIONS

The combination of structural and computational analysis has been carried out throughout this work in order to understand π-holes interactions in experimental and model-based lactam systems.

From this extensive investigation, several conclusions can be addressed:

- It has been observed that in carbonyl-carbonyl π-hole interactions there is both an electrostatic and orbital contribution unlike what was until recently understood, where it was thought that such interactions where merely driven by electrostatic forces.
- DFT and NBO calculations at the M06-2X/def2-TZVP level have shown that orbital contribution, even if it is small, plays a key role in the formation of crystalline structure since structural parameters, such as the attack angle, are driven by it.
- MEP and AIM analysis have showcased the electrostatic component in π-hole interactions.
- Also, other secondary interactions have been observed which also contribute to the overall stability of the studied cases, such as intermolecular N—H···O=C and C_{ring}—H_{ring}···O=C interactions with interaction energies in some cases higher than the carbonyl-carbonyl interaction.

8. REFERENCES AND NOTES

1. Fernandes, R., Amador, P. & Prudêncio, C. β-Lactams: Chemical structure, mode of action and mechanisms of resistance. *Rev. Med. Microbiol.* **24**, 7–17 (2013).
2. Baldwin, J. E., Lynch, G. P. & Pitlik, J. Γ-Lactam Analogues of B-Lactam Antibiotics. *J. Antibiot. (Tokyo).* **44**, 1–24 (1991).
3. Groom, C. R., Bruno, I. J., Lightfoot, M. P. & Ward, S. C. The Cambridge structural database. *Acta Crystallogr. Sect. B Struct. Sci. Cryst. Eng. Mater.* (2016).
4. Alvarez, S. A cartography of the van der Waals territories. *Dalt. Trans.* **42**, 8617–8636 (2013).
5. Nathan, A. J. & Scobell, A. Gaussian09. *Foreign Aff.* (2012).
6. Zhao, Y. & Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: Two new functionals and systematic testing of four M06-class functionals and 12 other function. *Theor. Chem. Acc.* **120**, 215–241 (2008).
7. Boys, S. F. & Bernardi, F. The calculation of small molecular interactions by the differences of separate total energies. Some procedures with reduced errors. *Mol. Phys.* (1970).
8. Murray, J. S., Lane, P., Clark, T., Riley, K. E. & Politzer, P. σ-Holes, π-holes and electrostatically-driven interactions. *J. Mol. Model.* **18**, 541–548 (2012).
9. Sjoberg, P. & Politzer, P. Use of the electrostatic potential at the molecular surface to interpret and predict nucleophilic processes. *J. Phys. Chem.* **94**, 3959–3961 (1990).
10. Jabłoński, M. On the Uselessness of Bond Paths Linking Distant Atoms and on the Violation of the Concept of Privileged Exchange Channels. *ChemistryOpen* (2019).
11. Reed, A. E., Curtiss, L. A. & Weinhold, F. Intermolecular Interactions from a Natural Bond Orbital, Donor—Acceptor Viewpoint. *Chem. Rev.* **88**, 899–926 (1988).
12. Weinhold, F. & Landis, C. R. *Discovering Chemistry with Natural Bond Orbitals*. *Discovering Chemistry with Natural Bond Orbitals* (2012).
13. Bader, R. F. W. Atoms in Molecules: A Quantum Theory, International Series of Monographs on Chemistry 22. *Oxford Univ. Press. Oxford Henkelman G, Arnaldsson A, Jónsson H A fast robust algorithm Bader Decompos. Charg. density. Comput Mater Sci* (1990).
14. Keith, T. A. AIMALL (Version 19.02.13). *AIMALL (Version 19.02.13), TK Gristmill Software, Overl. Park KS, USA,* (2019).
15. Velásquez, J. D., Echeverriá, J. & Alvarez, S. Effect of the Substituents on the Nature and Strength of Lone-Pair-Carbonyl Interactions in Acyl Halides. *Cryst. Growth Des.* **19**, 6511–6518 (2019).
16. Newberry, R. W. & Raines, R. T. The n→π∗ Interaction. *Acc. Chem. Res.* **50**, 1838–1846 (2017).
17. Biirgi, H. B., Dunitz, J. D. & Shefter, E. Geometrical Reaction Coordinates. II. Nucleophilic Addition to a Carbonyl Group. *J. Am. Chem. Soc.* **95**, 5065–5067 (1973).
18. B:urgi, H. B., Dunitz, J. D., Lehn, J. M. & Wipff, G. Stereochemistry of reaction paths at carbonyl centres. *Tetrahedron* (1974).
19. Echeverría, J. Noncovalent Interactions in Succinic and Maleic Anhydride Derivatives. *Cryst. Growth Des.* **18**, 506–512 (2018).
20. Echeverriá, J., Velásquez, J. D. & Alvarez, S. Understanding the Interplay of Dispersion, Charge Transfer, and Electrostatics in Noncovalent Interactions: The Case of Bromine-Carbonyl Short Contacts. *Cryst. Growth Des.* (2020).
21. Singh, S. K. & Das, A. The n → π∗ interaction: A rapidly emerging non-covalent interaction. *Phys. Chem. Chem. Phys.* **17**, 9596–9612 (2015).
22. Wang, H., Wang, W. & Jin, W. J. σ-Hole Bond vs π-Hole Bond: A Comparison Based on Halogen Bond. *Chem. Rev.* **116**, 5072–5104 (2016).
23. Hanwell, M. D. *et al.* Avogadro: An advanced semantic chemical editor, visualization, and

analysis platform. *J. Cheminform.* (2012).
24. Hilal, R., Aziz, S. G., Alyoubi, A. O. & Elroby, S. Quantum topology of the charge density of chemical bonds. QTAIM analysis of the C-Br and O-Br bonds. *Procedia Comput. Sci.* **51**, 1872–1877 (2015).
25. Fradera, X., Austen, M. A. & Bader, R. F. W. The Lewis Model and Beyond. *J. Phys. Chem. A* **103**, 304–314 (1999).
26. Wang, Y. G., Matta, C. & Werstiuk, N. H. Comparison of Localization and Delocalization Indices Obtained with Hartree-Fock and Conventional Correlated Methods: Effect of Coulomb Correlation. *J. Comput. Chem.* **24**, 1720–1729 (2003).
27. Yourdkhani, S., Jabłoński, M. & Echeverría, J. Attractive PH···HP interactions revealed by state-of-the-art: Ab initio calculations. *Phys. Chem. Chem. Phys.* **19**, 28044–28055 (2017).
28. Velásquez, J. D. *et al.* Experimental and theoretical study of Pb···S and Pb···O σ-hole interactions in the crystal structures of Pb(ii) complexes. *CrystEngComm* **21**, 6018–6025 (2019).

9. ACRONYMS

AIM: Atoms In Molecules

AO: Atomic Orbitals

B3LYP: Hybrid functional, “Becke, 3-parameter, Lee-Yang-Parr”

BCP: Bond Critical Point

BSSE: Basis Set Superposition Error

CSD: Cambridge Structural Database

CP: Counterpoise

DC: Dicoordinated

def2-TZVP: Karlsruhe basis set, Valence triple-zeta polarization

DFT: Density Functional Theory

GGA: Generalized Gradient Approximation

HF: Hartree-Fock

LDA: Local-Density Approximation

MC: Monocoordinated

MEP: Molecular Electrostatic Potential

MO: Molecular Orbital

NBO: Natural Bond Orbital

APPENDICES

APPENDIX 1: INTERACTION ENERGY – ANGLE Β CORRELATION ANALYSIS

	Angle β (°)	ΔE_{int} (kcal·mol^{-1})
β-lactam	90	-8.12
	120	-4.64
	135	-3.63
	150	-2.92
	180	-1.86
γ-lactam	120	-8.60
	127.5	-6.93
	135	-5.58
	150	-3.76
	180	-2.09
δ-lactam	120	-9.54
	127.5	-7.73
	135	-6.15
	150	-3.99
	180	-2.2

	110.9	-10.8
	120	-8.93
ε-lactam	135	-5.56
	150	-3.42
	180	-1.56

Table A1. Resultant interaction energies obtained from the angle β scan

APPENDIX 2: SECOND-ORDER PERTURBATION ENERGY ANALYSIS FOR CARBONYL-CARBONYL INTERACTIONS

Carbonyl-Carbonyl interaction system	Charge transfer interaction	$E^{(2)}$ (kcal/mol)
β-lactam	$\pi \rightarrow \pi^*$	0.05
	$\pi \rightarrow \pi^*$	0.65
γ-lactam	$n \rightarrow \pi^*$	0.31
	$n \rightarrow \pi^*$	0.88
δ-lactam	$n \rightarrow \pi^*$	0.05
	$n \rightarrow \pi^*$	1.19
ε-lactam	$n \rightarrow \pi^*$	0.3
	$n \rightarrow \pi^*$	0.62
BOVFOH	$n \rightarrow \pi^*$	0.25
	$n \rightarrow \pi^*$	0.06
DEDSIO	$n \rightarrow \pi^*$	0.16
	$n \rightarrow \pi^*$	0.10
	$n \rightarrow \pi^*$	0.10
	$n \rightarrow \pi^*$	0.16

FIYCOG	$\pi \rightarrow \pi^*$	0.34
	$n \rightarrow \pi^*$	0.21
	$\pi \rightarrow \pi^*$	0.32
	$\pi \rightarrow \pi^*$	0.10
	$n \rightarrow \pi^*$	0.19
KUJJOO	$\pi \rightarrow \pi^*$	0.17
	$\pi \rightarrow \pi^*$	0.17
UMUNAS	$n \rightarrow \pi^*$	0.88
	$n \rightarrow \pi^*$	0.41

Table A2. Second-Order perturbation energies along with their related charge transfer interaction